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ART UNIT	**PAPER NUMBER**
1655	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/269,598	LIPSKY ET AL.	
	Examiner	Art Unit	
	MELENIE MCCORMICK	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *9-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 21-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/02/2008 & 08/24/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-8 and 21-39) in the reply filed on 12/07/2010 is acknowledged.

Claims 9-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-8 and 21-39 are presented for examination on the merits.

Information Disclosure Statement

The Information Disclosure Statements submitted 08/24/2000 and 09/02/2008 have been received and considered.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 and 21-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,294,443 in view of Lian et al. (1989), Wiedmann et al. (WO 9513082) and Su et al. (1990).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '443 are drawn to a method for suppressing interleukin-2 in autoimmune disease comprising administering a preparation consisting essentially of a *Tripterygium wilfordii* Hook F root extract in a therapeutically effective amount to a patient having an autoimmune disease sufficient to suppress interleukin-2 production (see e.g. claim 2). As disclosed by the instant specification, *Tripterygium wilfordii* Hook F root extracts bind to the glucocorticoid receptor and that complex inhibits transcription of certain genes such as IL-2, IFN gamma and COX-2 (see e.g. page 8). Therefore, the claims of '443 teach a method of inhibiting interleukin-2 gene transcription and a method of treating an autoimmune disease, as instantly claimed. The claims of '443 further teach that the autoimmune disease is rheumatoid arthritis, systemic lupus erythematosus or psoriasis (see e.g. claim 3). The claims of '443 further teach that the therapeutically effective amount is 60 mg/day (see e.g. claim 8). The steroid sparing effect defined by instant claims 6-7 would necessarily occur because the same amount of the same composition (i.e. 60 mg per day of an extract of *Tripterygium wilfordii* Hook F root) was administered to the same patient population as instantly claimed. Therefore, the ability to administer less prednisone to a patient due to the method disclosed by the claims of '443 would necessarily be present. It should be noted that the instant claims do not require the administration of prednisone.

The claims of '443 do not explicitly teach that the extract administered in an ethanol extract, a chloroform-ethanol extract, that the extract contains triptolide or wilforonide, that triptolide is present in the amounts instantly claimed or that the extract

has the particular LD_{50} values, therapeutic activity: toxic index ratios or an ID_{50} in vitro T-cell proliferation/ LD_{50} ratio as instantly claimed.

Lian et al. teach that T2, which known in the art as the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F (see e.g. page 3, instant specification), is effective in treating rheumatoid arthritis (see e.g. entire article and discussion, pages 330-333).

Wiedmann et al. teach an ethanol extract of *Tripterygium wilfordii* Hook F root which has immunosuppressive activity (see e.g. page 4, lines 20-31 and page 7, lines 10-30). Wiedmann et al. further teach that the extract is useful for treating a number of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythermatosus and psoriasis (see e.g. page 14-15).

Su et al. teach that an ethyl acetate extract of *Tripterygium wilfordii* (TW) was used to treat rheumatoid arthritis. Su et al. further teach that the ethyl acetate extract was the effective part of TW. Su et al. further teach that although rheumatoid arthritis was treated using triptolide, the ethyl acetate extract of TW was as effective and that triptolide could impair some patient's hearts. Su et al. teach that triptolide is one of the main effective components of TW, but it is also one of the main toxic elements. Su et al. further teach that clinical research indicated that the effect of TW in treating rheumatoid arthritis was the synergistic action of elements with triptolide as the main active and that triptolide may act as a major standard of controlling the quality of the preparation of TW and assure use safely (see e.g. English abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a chloroform-ethanol extract in the method of

treating rheumatoid arthritis disclosed in the claims of ‘443. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Lian et al. that such an extract was useful for this purpose. Since the instant specification discloses that the extract contains both triptolide and wilforonide (see e.g. page 4), the extract used in the method rendered obvious by the claims of '443 and Lian et al. would also contain these compounds. Since it would have been obvious to use a chloroform -ethanol extract of *Tripterygium wilfordii* Hook F root in the method disclosed in the claims of ‘443, the patients would receive the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root (which would be capable of binding glucocorticoid receptor because it is the same extract as instantly claimed and is the same extract as disclosed in the specification at pages 68-69 as being capable of binding the glucocorticoid receptor) in the same amount as instantly claimed. Therefore inhibition of cyclooxygenase-2 induction, wherein cyclooxygenase-1 is substantially unaffected would necessarily occur. With regard to the limitation ‘wherein inhibiting cyclooxygenase-2 induction inhibits synthesis of a prostaglandin, an autacoid, or a cytokine inhibited by glucocorticoids, this functional effect would necessarily occur as a result of the inhibition of cyclooxygenase-2 induction. In addition, administration of the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root would also block interferon gamma production in the patients since the instant specification discloses that T2, the same extract used in the method rendered obvious by the claims of ‘443 and Lian et al., inhibits interferon gamma gene activation (see e.g. page 68).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use an ethanol extract in the method disclosed by the claims of '443. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Wiedmann et al. that an ethanol extract of *Tripterygium wilfordii* Hook F root has immunosuppressive activity and is useful for rheumatoid arthritis, systemic lupus erythematosus. Therefore, a person of ordinary skill in the art would have been motivated to administer an effective amount of an ethanol extract of *Tripterygium wilfordii* Hook F root to a subject for treating the immune diseases arthritis, systemic lupus erythematosus and psoriasis since Wiedmann et al. teaches that such an extract is immunosuppressive and is useful for treating these diseases. Since the extract is an ethanol extract, as instantly claimed, it would necessarily have anti-inflammatory and immunosuppressive pharmacological activity and provide for a steroid-sparing effect, as instantly claimed.

It would have further been obvious to one of ordinary skill in the art at the time the claimed invention was made to use an ethyl acetate extract of *Tripterygium wilfordii* Hook F root in the method of treating rheumatoid arthritis disclosed by the claims of '443. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Su et al. that such an extract is useful in treating rheumatoid arthritis. Since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has the LD_{50} ranges as instantly claimed (see e.g. page 50), it would be reasonably expected that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root used in a method as rendered obvious by

the claims of '443 and Su et al. would also have these LD_{50} ranges in mice. Likewise, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has therapeutic activity: toxic activity ratios as instantly claimed (see e.g. page 10), it would be expected that the ethyl acetate extract used in the method rendered obvious by the claims of '443 and Su et al. would also have these therapeutic activity: toxic activity ratios. In addition, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has an *in vitro* T-cell proliferation/ LD_{50} ratio greater than about $2.6X10^{-3}$, it would be expected that the ethyl acetate extract used in the method rendered obvious by the claims of '443 and Su et al. would also have this *in vitro* T-cell proliferation/ LD_{50} ratio. In addition, since Su et al. et al. disclose that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root is less toxic than triptolide (one of the components of the extract) and since Su et al. disclose that triptolide is therapeutically effective but toxic, it would have been obvious to adjust the amount of triptolide in the extract administered to treat rheumatoid arthritis in order to optimize the therapeutic benefit of triptolide and minimize its toxicity. The administration of *Tripterygium wilfordii* Hook F root as rendered obvious by the Su et al. and the claims of '443 would result in inhibition of cyclooxygenase-2 induction and the extract would be capable of binding a glucocorticoid receptor, instantly claimed since the instant specification discloses that such an extract has this effect (see e.g. claim 10).

Claims 1-7, 21-23, and 25-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,580,562 in view of Su et al.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '562 are drawn to a *Tripterygium wilfordii* Hook F root preparation having a triptolide concentration of about 0.2 to about 1.3 µg/mg and having an LD_{50} in mice of about 860 to about 1300 mg/kg (see e.g. claim 1). The claims of '562 are further drawn to the composition wherein the LD_{50} in mice is about 1250 mg/kg (see e.g. claim 2). The claims of '562 are further drawn to the composition wherein the composition has a therapeutic activity: toxic index ratio from about $2.6X10^{-3}$ (see e.g. claim 3), a therapeutic activity: toxic index ratio from about $2.6X10^{-3}$ to about $4.5X10^{-3}$ (see e .g. claim 4) or a therapeutic activity: toxic index ratio of about $4.5X10^{-3}$ (see e.g. claim 5). The claims of '562 are further drawn to the composition wherein the extract is an ethyl acetate extract (see e.g. claim 9).

The claims of '562 do not explicitly teach administration of this composition to treat rheumatoid arthritis or to inhibit cyclooxygenase-2 induction, block interferon gamma production or inhibit interleukin-2 gene transcription.

Su et al. teach that an ethyl acetate extract of *Tripterygium wilfordii* (TW) was used to treat rheumatoid arthritis. Su et al. further teach that the ethyl acetate extract was the effective part of TW. Su et al. further teach that although rheumatoid arthritis was treated using triptolide, the ethyl acetate extract of TW was as effective and that

triptolide could impair some patient's hearts. Su et al. teach that triptolide is one of the main effective components of TW but it is also one of the main toxic elements. Su et al. further teach that clinical research indicated that the effect of TW in treating rheumatoid arthritis was the synergistic action of elements with triptolide as the main active and that triptolide may act as a major standard of controlling the quality of the preparation of TW and assure use safely (see e.g. English abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the ethyl acetate extract of *Tripterygium wilfordii* Hook F root disclosed in the claims of '562 in the method of treating rheumatoid arthritis disclosed by Su et al. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Su et al. that such an ethyl acetate extract of *Tripterygium wilfordii* Hook F root is useful in treating rheumatoid arthritis. In addition, since Su et al. et al. disclose that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root is less toxic than triptolide (one of the components of the extract) and since Su et al. discloses that triptolide is therapeutically effective but toxic, it would have been apparent to one of ordinary skill in the art that an effective, yet non-toxic *Tripterygium wilfordii* Hook F root extract would be desirable for use in the method disclosed by Su et al. Therefore, it would have been obvious to one of ordinary skill in the art to employ the ethyl acetate extract disclosed by the claims of '562, which is disclosed as having low toxicity (in light of the disclosure of the therapeutic activity: toxicity ratios). The administration of the *Tripterygium wilfordii* Hook F root extract as rendered obvious by the claims of '562 and Su et al. would result in inhibition of

cyclooxygenase-2 induction and the extract would be capable of binding a glutocorticoid receptor, as instantly claimed since the instant specification discloses that such an extract has this effect (see e.g. pages 11-12). The extract would have anti-inflammatory and immune suppressive effects since the instant specification discloses that such an extract has theses effects (see e.g. page 83). The steroid sparing effect would necessarily result from treatment with the extract (i.e. since the extract is therapeutic, less steroid would be required). In addition, gamma interferon production and interleukin-2 gene transcription would be expected to inhibited upon administration of the extract since the instant specification discloses that this extract has these effects (see e.g. pages 11-13). Since the instant specification discloses that wilforonide can be isolated from an ethyl acetate extract of *Tripterygium wilfordii* Hook F root, the ethyl acetate extract used in the method rendered obvious by the claims of '562 and Su et al. would contain this compound.

Claims 1-8 and 21-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,916,564 in view of Lian et al. (1989) and Su et al. (1990).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '564 are drawn to a method of immunosuppression and suppressing an autoimmune disease comprising administering *Tripterygium wilfordii* Hook F root extract in a therapeutically effective amount to a

patient in need of such treatment, said amount inhibiting interleukin-2 production without substantial cellular toxicity (see e.g. claims 1 and 3). The claims of '564 also teach that the preparation comprises tripdiolide or triptolide (see e.g. claim 2). The claims of '564 are also drawn to the method of immunosuppression wherein the subject has an autoimmune disease which may be rheumatoid arthritis, systemic lupus erythematosus or psoriasis (see e.g. claim 4). The claims of '564 teach that the therapeutically effective amount is about 60 mg/kg/day (see e.g. claim 8). The claims of '564 are also drawn to a method of treating inflammation or immune disease in a subject comprising administering to the subject a pharmacologically active amount of a *Tripterigium wilfordii* F root extract, the preparation having anti-inflammatory and immunosuppressive pharmacological activity, and a steroid, wherein the method provides a steroid sparing effect, wherein the steroid is prednisone (see e.g. claims 11 and 17). The claims of '564 are further drawn to the method wherein the immune disease is an autoimmune disease, specifically, rheumatoid arthritis, systemic lupus erythematosus or psoriasis (see e.g. claim 13). The claims of '564 are further drawn to the method wherein the extract is an ethanol extract of *Tripterigium wilfordii* (see e.g. claim 18).

The claims of '564 do not explicitly teach that the extract of *Tripterigium wilfordii* contains wilforonide, that the extract is a chloroform-ethanol extract *Tripterigium wilfordii* , that triptolide is present in the amounts instantly claimed or that the extract has the particular LD_{50} values, therapeutic activity: toxic index ratios or an ID_{50} *in vitro* T-cell proliferation/ LD_{50} ratio as instantly claimed.

Lian et al. teach that T2, which known in the art as the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F (see e.g. page 3, instant specification), is effective in treating rheumatoid arthritis (see e.g. entire article and discussion, pages 330-333).

Su et al. teach that an ethyl acetate extract of *Tripterygium wilfordii* (TW) was used to treat rheumatoid arthritis. Su et al. further teach that the ethyl acetate extract was the effective part of TW. Su et al. further teach that although rheumatoid arthritis was treated using triptolide, the ethyl acetate extract of TW was as effective and that triptolide could impair some patient's hearts. Su et al. teach that triptolide is one of the main effective components of TW but it is also one of the main toxic elements. Su et al. further teach that clinical research indicated that the effect of TW in treating rheumatoid arthritis was the synergistic action of elements with triptolide as the main active and that triptolide may act as a major standard of controlling the quality of the preparation of TW and assure use safely (see e.g. English abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a chloroform-ethanol extract in the method of treating rheumatoid arthritis disclosed in the claims of '564. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Lian et al. that such an extract was useful for this purpose. Since the instant specification discloses that the extract contains wilforonide (see e.g. page 4), the extract used in the method rendered obvious by the claims of '564 and Lian et al. would also contain this compound. Since it would have been obvious to use a chloroform ethanol extract of *Tripterygium wilfordii* Hook F root in the method disclosed in the

claims of '564, the patients would receive the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root (which would be capable of binding glucocorticoid receptor because it is the same extract as instantly claimed and is the same extract as disclosed in the specification at pages 68-69 as being capable of binding the glucocorticoid receptor) in the same amount as instantly claimed. Therefore inhibition of cyclooxygenase-2 induction, wherein cyclooxygenase-1 is substantially unaffected would necessarily occur. With regard to the limitation 'wherein inhibiting cyclooxygenase-2 induction inhibits synthesis of a prostaglandin, an autacoid, or a cytokine inhibited by glucocorticoids, this functional effect would necessarily occur as a result of the inhibition of cyclooxygenase-2 induction. In addition, administration of the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root would also block interferon gamma production in the patients since the instant specification discloses that T2, the same extract used in the method rendered obvious by the claims of '564 and Lian et al., inhibits interferon gamma gene activation (see e.g. page 68).

It would have further been obvious to one of ordinary skill in the art at the time the claimed invention was made to use an ethyl acetate extract of *Tripterygium wilfordii* Hook F root in the method of treating rheumatoid arthritis disclosed by the claims of '564. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Su et al. that such an extract is useful in treating rheumatoid arthritis. Since the instant specification discloses that ethyl acetate extract of *Tripterygium wilfordii* Hook F root have the LD_{50} ranges as instantly claimed (see e.g. page 50), it would be reasonably expected that an ethyl acetate

extract of *Tripterygium wilfordii* Hook F root used in a method as rendered obvious by the claims of '564 and Su et al. would also have these LD_{50} ranges in mice. Likewise, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has therapeutic activity: toxic activity ratios as instantly claimed (see e.g. page 10), it would be expected that the ethyl acetate extract used in the method rendered obvious by the claims of '564 and Su et al. would also have these therapeutic activity: toxic activity ratios. In addition, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has an *in vitro* T-cell proliferation/ LD_{50} ratio greater than about $2.6X10^{-3}$, it would be expected that the ethyl acetate extract used in the method rendered obvious by the claims of '564 and Su et al. would also have this *in vitro* T-cell proliferation/ LD_{50} ratio. In addition, since Su et al. et al. disclose that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root is less toxic than triptolide (one of the components of the extract) and since Su et al. disclose that triptolide is therapeutically effective but toxic, it would have been obvious to adjust the amount of triptolide in the extract administered to treat rheumatoid arthritis in order to optimize the therapeutic benefit of triptolide and minimize its toxicity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 21-27 and 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipsky et al. (US 5,294,443).

Lipsky et al. teach a method for inhibiting interleukin-2 in autoimmune disease comprising administering a preparation consisting essentially of a *Tripterygium wilfordii* Hook F root extract in a therapeutically effective amount to a patient having an autoimmune disease sufficient to suppress interleukin-2 production (see e.g. claim 2). Lipsky et al. disclose that interleukin-2 production is inhibited due to inhibition of gene transcription (see e.g. col 5, lines 51-53). Therefore, Lipsky et al. teach a method of inhibiting interleukin-2 gene transcription and a method of an autoimmune disease, as instantly claimed. Lipsky et al. further teach that the autoimmune disease is rheumatoid arthritis, systemic lupus erythematosus or psoriasis (see e.g. claim 3). Lipsky et al. further teach that the therapeutically effective amount is 60 mg/day (see e.g. claim 8). Lipsky et al. further teach a particular embodiment wherein rheumatoid arthritis patients (i.e. patients with an autoimmune disease) are treated with 60 mg per day of an extract of *Tripterygium wilfordii* Hook F root, which is a mixture of compounds extracted from T *Tripterygium wilfordii* Hook F and is referred to as “T2” (see e.g. col 11, Example 3).

Lipsky et al. teach that T2 is a chloroform ethanol extract of the woody potion of *Tripterygium wilfordii* Hook F root (see e.g. page col 1, lines 40-42) and that the extract contains components including triptolide and wilforonide (see e.g. col 2, lines 48-52). In addition, Lipsky et al. teach that rheumatoid arthritis patients treated with T2 showed improvement in different clinical criteria or laboratory correlates of inflammation and that an immunosuppressive activity was implicated by the finding that the treatment induced inhibition of the production of IgM and IgM rheumatoid factor by the patient's peripheral blood mononuclear cells in vitro (see e.g. col 1, lines 49-62 and col 15, lines 52-62). Therefore, Lipsky et al. teach a method for treating inflammation and an immune disease in a subject comprising administering to the subject a pharamcalogically effective amount of a *Tripterygium wilfordii* Hook F root preparation, the preparation having anti-inflammatory and immunosuppressive activity, as instantly claimed. Lipsky et al. further teach that a steroid sparing effect was noted (see e.g. col 15, lines 65-66). The steroid sparing effect defined by claims 6-7 would necessarily be possible because the same amount of the same composition (i.e. 60 mg per day of an extract of *Tripterygium wilfordii* Hook F root) was administered to the same patient population as instantly claimed. Therefore, the ability to administer less prednisone to a patient due to the method disclosed by Lipsky et al. would necessarily be present. It should be noted that the instant claims do not require the administration of prednisone.

The patients disclosed by Lipsky et al. are administered a chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root (which would be capable of binding glucocorticoid receptor because it is the same extract as instantly claimed and is the

same extract as disclosed in the specification at pages 68-69 as being capable of binding the glucocorticoid receptor) in the same amount as instantly claimed, therefore inhibition of cyclooxygenase-2 induction, wherein cyclooxygenase-1 is substantially unaffected would necessarily occur. With regard to the limitation 'wherein inhibiting cyclooxygenase-2 induction inhibits synthesis of a prostaglandin, an autacoid, or a cytokine inhibited by glucocorticoids, this functional effect would necessarily occur as a result of the inhibition of cyclooxygenase-2 induction. In addition, administration of the chloroform-ethanol extract of *Tripterygium wilfordii* Hook F root would also block interferon gamma production in the patients since the instant specification discloses that T2, the same extract used in the method disclosed by Lipsky et al., inhibits interferon gamma gene activation (see e.g. page 68).

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 21-27 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipsky et al. in view of Wiedman et al. (WO 9513082).

Lipsky et al. teach a method for treating inflammation or immune disease (including the autoimmune diseases rheumatoid arthritis, systemic lupus erythermatosus and psoriasis) in a subject comprising administering to the subject a pharmacologically active amount of a *Tripterygium wilfordii* Hook F root preparation, the preparation having anti-inflammatory and immunosuppressive pharmacological activity, wherein said method provides a steroid sparing effect and is relied upon for the reasons set forth above.

Lipsky et al. does not explicitly teach that the extract is an ethanol extract.

Wiedmann et al. teach an ethanol extract of *Tripterygium wilfordii* Hook F root which has immunosuppressive activity (see e.g. page 4, lines 20-31 and page 7, lines 10-30). Wiedmann et al. further teach that the extract is useful for treating a number of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythermatosus and psoriasis (see e.g. page 14-15).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use an ethanol extract in the method disclosed by Lipsky et al. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Wiedmann et al. that an ethanol extract of *Tripterygium wilfordii* Hook F root has immunosuppressive activity and is useful for treating rheumatoid arthritis, systemic lupus erythermatosus and psoriasis. Therefore, a person of ordinary skill in the art would have been motivated to administer an effective amount of an ethanol extract of *Tripterygium wilfordii* Hook F root to a subject for treating the immune diseases arthritis, systemic lupus

erythematosus and psoriasis since Wiedmann et al. teaches that such an extract is immunosuppressive and is useful for treating these diseases. Since the extract is an ethanol extract, as instantly claimed, it would necessarily have anti-inflammatory and immunosuppressive pharmacological and provide for a steroid-sparing effect, as instantly claimed.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-7 and 21-39 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Lipsky et al. (US 5,294,443) in view of Su et al (1990).

Lipsky et al. teach a method a method for inhibiting cyclooxygenase-2 induction in a subject comprising administering to the subject a pharmaceutically active amount of a *Tripterygium wilfordii* Hook F root preparation, or a pharmacologically active component thereof, capable of binding glucocorticoid receptor and a method of treating inflammation or immune disease (including the autoimmune disease is rheumatoid arthritis, systemic lupus erythermatosus or psoriasis) in a subject comprising administering to the subject a pharmacologically active amount of a *Tripterygium wilfordii* Hook F root preparation and is relied upon for the reasons set forth above. As

discussed above, Lipsky et al. disclose an example wherein rheumatoid arthritis is treated using a *Tripterygium wilfordii* Hook F root chloroform-ethanol extract. Lipsky et al. also teach that experiments conducted indicated that triptolide has therapeutic activity at small concentrations but that triptolide is also very toxic (see e.g. cols 16-17). Lipsky et al. also teach that purified components from the chloroform- ethanol extract of *Tripterygium wilfordii* Hook F root (T2) will be administered to patients with autoimmune diseases and inflammatory diseases including rheumatoid arthritis and that the dosage will be determined based up the concentration of each component in the crude mixture (see e.g. col 17, lines 22-25).

Lipsky et al. do not explicitly teach that the preparation has an LD_{50} in mice of greater than about 860 mg/kg, from about 860 mg/kg to about 1300 mg/kg, or about 1250 mg/kg. Lipsky et al. also do not explicitly teach that the preparation has a therapeutic activity:toxic index ratio of about 2.6×10^{-3} from, about 2.6×10^{-3} to about 4.5×10^{-3}, about 4.5×10^{-3} or that the preparation has an ID_{50} in vitro T-cell proliferation/LD_{50} greater than about $2.6X10^{-3}$. Lipsky et al. also do not explicitly teach that the preparation has the particular amounts of triptolide as instantly claimed.

Su et al. teach that an ethyl acetate extract of *Tripterygium wilfordii* (TW) was used to treat rheumatoid arthritis. Su et al. further teach that the ethyl acetate extract was the effective part of TW. Su et al. further teach that although rheumatoid arthritis was treated using triptolide, the ethyl acetate extract of TW was as effective and that triptolide could impair some patient's hearts. Su et al. teach that triptolide is one of the main effective components of TW but it is also one of the main toxic elements. Su et al.

further teach that clinical research indicated that the effect of TW in treating rheumatoid arthritis was the synergistic action of elements with triptolide as the main active and that triptolide may act as a major standard of controlling the quality of the preparation of TW and assure use safely (see e.g. English abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use an ethyl acetate extract of *Tripterygium wilfordii* Hook F root in the method of treating rheumatoid arthritis disclosed by Lipsky et al. A person of ordinary skill in the art would have had a reasonable expectation of success in doing so based upon the disclosure of Su et al. that such an extract is useful in treating rheumatoid arthritis. Since the instant specification discloses that ethyl acetate extract of *Tripterygium wilfordii* Hook F root has the LD_{50} ranges as instantly claimed (see e.g. page 50), it would be reasonably expected that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root used in a method as rendered obvious by Lipsky et al. and Su et al. would also have these LD_{50} ranges in mice. Likewise, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has therapeutic activity: toxic activity ratios as instantly claimed (see e.g. page 10), it would be expected that the ethyl acetate extract used in the method rendered obvious by Lipsky et al. and Su et al. would also have these therapeutic activity: toxic activity ratios. In addition, since the instant specification discloses that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root has an *in vitro* T-cell proliferation/ LD_{50} ratio greater than about $2.6X10^{-3}$, it would be expected that the ethyl acetate extract used in the method rendered obvious by Lipsky et al. and Su et al. would also have this *in vitro* T-

cell proliferation/ LD_{50} ratio. In addition, since Su et al. et al. disclose that an ethyl acetate extract of *Tripterygium wilfordii* Hook F root is less toxic than triptolide (one of the components of the extract) and since both Lipsky et al. and Su et al. disclose that triptolide is therapeutically effective but toxic, it would have been obvious to adjust the amount of triptolide in the extract administered to treat rheumatoid arthritis in order to optimize the therapeutic benefit of triptolide and minimize its toxicity.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELENIE MCCORMICK whose telephone number is (571)272-8037. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Melenie McCormick/
Examiner, Art Unit 1655